Claims 103, 107, 109 and 122 have been amended and Claims 113 and 120 have been further amended to more particularly point out that the MAdCAM has the recited percentage amino acid sequence similarity. Support for the amendments is found at page 17, lines 23-29, for example.

Claim 107 has been amended to recite "said $\alpha 4\beta 7$ integrin-binding fragment comprises the N-terminal immunoglobulin-like domain of said primate MAdCAM," and Claims 126 and 131 have been amended to recite "wherein said $\alpha 4\beta 7$ integrin-binding portion comprises the N-terminal immunoglobulin-like domain." Support for the amended claims is found at page 19, lines 11-18, for example.

Support for new Claims 136-160 is found throughout the application as filed, for example, at page 16, lines 25-31; page 17, lines 23-29; page 19, lines 11-18 and Example 3 (pages 70-76).

The amended claims and new claims are supported by the application as filed. Therefore, this Amendment adds no new matter. Additional remarks are presented below with reference to the numbered paragraphs of the Office Action.

Paragraph 5. Rejection of Claims 24-26, 28-32, 102-116 and 118-135 Under 35 U.S.C. § 112, First Paragraph

Claims 24-26, 28-32, 102-116 and 118-135 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. In the Examiner's opinion, the specification does not provide an adequate written description of the claimed fusion proteins containing primate MAdCAM. The Examiner states, "[i]n the instant application, the amino acid itself or isolated protein is required." Office Action at page 3, lines 11 and 12. Thus, the Examiner appears to suggest that an adequate written description of the claimed fusion proteins containing primate MAdCAM requires the disclosure of the amino acid sequences of all claimed primate MAdCAMs or of the isolated proteins. The Examiner cites Fiers v. Revel, 25 USPQ2d 1601

(Fed. Cir. 1993), Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 (Fed. Cir. 1991) and University of California v. Eli Lilly and Co., 43 USPQ2d 1398 (Fed. Cir. 1997) as supporting his position.

Cited Case Law

In Amgen, the court held that conception of a claimed gene requires that the inventor "be able to define it so as to distinguish it from other materials, and to describe how to obtain it." Amgen, 18 USPQ2d at 1021. The court stated that it is not sufficient to define a DNA solely by its principal biological property (i.e., the protein it encodes), but that conception occurs when "one has a mental picture of the structure of the chemical [DNA], or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it." Id. (emphasis added). Thus, Amgen specifically provides that conception of a claimed nucleic acid is not dependent on the inventor's ability to define the nucleic acid by its nucleotide sequence.

In Fiers, the court applied the Amgen standard of conception in determining priority of invention in a three party interference. The court also adopted the conception standard of Amgen for evaluating the sufficiency of written description stating, "[i]f a conception of a DNA requires a precise definition, such as by structure, formula, chemical name, or physical properties, as we have held, then a description also requires that degree of specificity." Fiers, 25 USPQ2d at 1603.

The Fiers interference involved a single count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

The court held that junior party Fiers was unable to establish a date of conception prior to the filing date of his application and did not address the written description requirement of 35 U.S.C. § 112. Fiers, 25 USPQ2d at 1604, 1605.

Junior party Revel attempted to establish priority based upon the filing date of his Israeli priority application, which disclosed a method for isolating a fragment of the DNA and a method for isolating a messenger RNA coding for Interferon-beta, but did not disclose a complete DNA

sequence coding for interferon-beta. Id. at 1603. In evaluating Revel's priority claim, the court focused on whether the Israeli application contained a written description of the DNA of the count. The court found that the Israeli application did not describe the DNA itself, and noted that the application did not even demonstrate that the disclosed methods would lead to the DNA. Id. The court held that Revel's Israeli application did not satisfy the written description requirement of 35 U.S.C. § 112. Id.

In contrast, senior party Sugano's Japanese priority application disclosed the complete nucleotide sequence of a DNA coding for interferon-beta and a method for isolating that DNA. Id. at 1603. The court concluded that "Sugano's application satisfies the written description requirement since it sets forth the complete and correct nucleotide sequence of a DNA coding for β-IF and thus 'convey[s] with reasonable clarity to those skilled in the art that, as of the filing date sought, [Sugano] was in possession of the [DNA coding for β-IF].'" Id. at 1607. Accordingly, the court affirmed the award of priority to Sugano. Id.

In Eli Lilly the court found claims of U.S. Patent No. 4,652,525 (the '525 patent), drawn to DNAs encoding vertebrate, mammalian or human insulin to be invalid for lack of an adequate written description of the claimed subject matter. The disclosure of the '525 patent includes the nucleotide sequence of a cDNA encoding rat insulin and a prophetic example teaching a method for isolating a cDNA encoding human insulin (U.S. Patent No. 4,652,525 at Examples 5-6). However, the patent does not include a description of the characteristics of any cDNAs encoding insulin other than rat insulin. The court held that a description of rat insulin cDNA is not a description of the claimed broader class of vertebrate, mammalian or human cDNA, stating:

> A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling withing the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.

Id. at 1406. The court recognized that adequate description of a genus of cDNAs can be achieved by distinguishing the members of the genus from other materials in other ways. However, the court did not speculate as to what other ways might be proper. Id.

Applicant's specification contains an adequate written description of the claimed subject matter and is readily distinguished from Fiers and Eli Lilly. In Fiers and Eli Lilly the court was looking at a generic count or generic claims which defined the claimed DNA solely by its biological function (i.e., encoding human fibroblast interferon-beta polypeptide, or vertebrate, mammalian or human insulin, respectively). In order to satisfy the written description requirement of 35 U.S.C. § 112 in those cases, the specifications needed to describe the DNA of the count or claim itself, for example, by structure, method of preparation, physical or chemical properties or whatever other characteristics distinguish the DNA from other materials.

In Fiers, junior party Revel's priority document did not describe the DNA of the count itself, but merely described methods purported to be suitable for isolating DNA. In contrast, Sugano's priority application described a DNA of the count by its structure, and thus satisfied the written description requirement of 35 U.S.C. § 112.

In Eli Lilly, the '525 patent disclosed a method purported to be suitable for isolating a DNA encoding human insulin and the amino acid sequence of rat insulin. However, the patent contains no description of any other DNA encoding insulin or of the broader class of DNAs encoding vertebrate, mammalian or human insulin. Therefore, the patent did not describe the claimed DNAs encoding vertebrate, mammalian or human insulin.

The subject application, unlike Revel's priority application in Fiers, discloses three primate MAdCAMs by amino acid sequence and three nucleic acids encoding primate MAdCAM by nucleotide sequence. Therefore, the disclosure of the subject application is similar to, but more extensive than that of Sugano's Japanese priority document, which the Federal Circuit held to satisfy the written description requirement of 35 U.S.C. § 112.

The subject application is also distinguished from the '525 patent in Eli Lilly which discloses a single species of DNA by nucleotide sequence, but contains no description of any other species of DNA or of the broader class of vertebrate, mammalian or human DNAs. In contrast, Applicants' specification specifically describes three species of primate MAdCAM by amino acid sequence, three nucleic acids encoding primate MAdCAM by nucleotide sequence, and describes the broader class of claimed fusion proteins comprising primate MAdCAM by a

combination of function (binds $\alpha 4\beta 7$ integrin) and structural features (amino acid sequence similarity) which are sufficient to distinguish the claimed nucleic acids from other materials. Specification at page 17, line 24 *et seq.*, for example.

The Examiner's Rationale for Maintaining the Rejection

In maintaining the rejection, Examiner states that there are 181 species encompassed by the term primate and that Applicants have not disclosed the amino acid sequence of the majority of primate MAdCAM proteins. Office Action at page 4, lines 22-26. The Examiner further states that it is unclear to him how defining the primate MAdCAM as having a recited amino acid sequence similarity to a reference amino acid sequence further describes the sequences of other primate variants, because the claims do not specify what particular regions of the sequence are similar and do not specify the identity of the nonsimilar portion. Office Action at page 5, lines 3-7.

The Examiner's remarks concerning the number of animal species considered to be primates appear to reflect the analysis employed by the Federal Circuit in Eli Lilly, where the claims defined a large genus of DNAs solely by their principal biological activity. In that case, disclosure of a single species of rat DNA was not sufficient to support generic claims to vertebrate, mammalian or human DNAs having the same principal biological activity. However, Eli Lilly did not create a rule that all members of the claimed genus of DNAs or even a representative number of species must be described by nucleotide sequence. In fact, the court in Eli Lilly recognized that a genus of cDNAs could be described other than by nucleotide sequence or structural features. Id.

With regard to the Examiner's statements regarding amino acid sequence similarity, the recitation of a particular degree of amino acid sequence similarity in a generic claim defines structural features that are common to members of the claimed genus. Eli Lilly expressly provides that written description of such a genus can be achieved by "a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id. (emphasis added) There is no requirement that additional features that are not necessary to distinguish the claimed fusion proteins from other materials, such as the nonsimilar

regions of the primate MAdCAM, be described in order to satisfy the written description requirement of 35 U.S.C. § 112.

The written description requirement is satisfied where the specification describes the claimed invention in sufficient detail so that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. Vas-Cath, Inc. v Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). The claims of the subject application, as amended, define the claimed fusion proteins comprising a primate MAdCAM by reciting function (binds $\alpha 4\beta 7$) and structural features (amino acid sequence identity) of the MAdCAM which distinguish the claimed fusion proteins from other materials. Therefore, a determination of whether the specification contains an adequate written description must focus on whether the specification conveys to those skilled in the art that Applicants were in possession of fusion proteins comprising primate MAdCAM having the properties recited in the claims when the application was filed.

Applicants' specification discloses three species of primate MAdCAM by amino acid sequence and three nucleic acids encoding primate MAdCAM by nucleotide sequence. The specification additionally describes preferred MAdCAMs as having an amino acid sequence that is at least about 55%, 75% or 90% similar to SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:6 (Specification at page 17, line 24 *et seq.*), preferred fragments of MAdCAM which bind $\alpha 4\beta 7$ integrin (Specification at page 16, lines 25-31, for example), and fusion proteins comprising the extracellular domain of MAdCAM or the two N-terminal immunoglobulin domains of MAdCAM (Specification at Example 3, pages 70-75) in sufficient detail so that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention at the time the application was filed. Therefore, following the standard of Fiers and Eli Lilly, the subject application provides adequate written description of the claimed invention.

The rejection is inconsistent with the Patent Office's understanding of the law and binding precedent as evidenced by Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, "Written Description" Requirement, 66 FR 1099 ("Guidelines") and associated training materials (available on line at

http://www.uspto.gov/web/offices/pac/writtendesc.pdf). It is acknowledged that the Guidelines and training materials do not have the force of law. However, because the rejection is based upon substantive patent law, it is appropriate to look to the Guidelines and training materials, and the analytical framework described and illustrated therein, for guidance in applying the substantive law to the facts of the case.

The written description requirement is satisfied where the specification describes the claimed invention in sufficient detail so that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. Vas-Cath, Inc. v Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). The Guidelines specifically provide that when a genus is claimed, the written description requirement may be satisfied by sufficient description of a representative number of species within the genus. Guidelines, 66 FR at 1106. If the genus encompasses species having substantial variation, a sufficient number of species that reflect the variation within the genus must be described. Id. However, where there is not substantial variation among species encompassed by the genus, description of a single species can adequately support claims to the genus. Id.

The training materials include examples which illustrate the application of substantive law to particular facts.

Example 14

Example 14 on page 53 of the training materials relates to written description of claims drawn to a protein and variants thereof which have a specified catalytic activity. In particular, in Example 14, the specification is said to disclose a single protein, that catalyzes the reaction A → B, by amino acid sequence (SEQ ID NO:3) and contemplates but does not exemplify variants having all or any of the following: substitutions, insertions and deletions. The specification is further said to indicate that procedures for producing such variants are conventional in the art and to disclose an assay for detecting the catalytic activity of the protein. The application is said to contain the following claim:

A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A → B.

The claim is drawn to a genus of proteins that are defined by function (catalyze the reaction of A → B) and structural features (SEQ ID NO:3, at least 95% identical to SEQ ID NO:3). The analysis presented in the Guidelines states that the claim has two generic embodiments 1) a protein which comprises SEQ ID NO:3; and 2) variants of SEQ ID NO:3.

Because a genus is claimed, the written description requirement may be satisfied by sufficient description of a representative number of species within the genus. The analysis present in Example 14 of the training materials, focuses on whether the specification satisfies the written description requirement by describing a representative number of species within the genus. "Satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." Guidelines, 66 FR at 1106.

According to the analysis, SEQ ID NO:3 is novel and nonobvious, and was actually reduced to practice. In addition, the specification and claim are said to reveal that:

1) the genus of proteins that are variants of SEQ ID NO:3 does not have substantial variation because all variants must have at least 95% identity to SEQ ID NO:3 and must have the specified activity; and

2) the single disclosed species (SEQ ID NO:3) is representative of the claimed genus because all members of the genus have at least 95% identity to SEQ ID NO:3 and because an assay suitable for identifying all variants that have the specified activity is disclosed.

Based on these findings, the specification in Example 14 of the training materials is said to meet the written description requirement of 35 U.S.C. § 112 for the claim.

The subject application is similar to Example 14 of the training materials in that the claims are drawn to a genus of fusion proteins that are defined by function (binds $\alpha 4\beta 7$ integrin) and structural features (SEQ ID NO. or % amino acid sequence similarity). However, the subject application contains a more extensive written description of the claimed invention than does the specification in Example 14 of the training materials. For example, the application discloses methods suitable for preparing fusion proteins comprising variants of primate MAdCAM, an assay for assessing binding to $\alpha 4\beta 7$ integrin and the reduction to practice of two species of the claimed fusion proteins. In addition, the application discloses three species of primate MAdCAM by amino acid sequence and describes the broader class of claimed fusion proteins comprising primate MAdCAM by describing a combination of function and structural features which are sufficient to distinguish the members of the genus from other materials.

Applying the analysis from Example 14 of the training materials to the subject application reveals:

1) the genus of fusion proteins that are variants of SEQ ID NOS: 2, 4 and or 6 does not have substantial variation because all variants must bind $\alpha 4\beta 7$ integrin and have at least the percentage of sequence similarity recited in the claims; and

2) the three disclosed species of primate MAdCAM (SEQ ID NOS: 2, 4 and 6) is representative of the claimed genus because all members of the genus have at least the percentage of amino acid sequence similarity to SEQ ID NOS:2, 4, and/or 6 recited in the claims, and an assay suitable for identifying all variants that have the specified activity is disclosed.

Therefore, like in Example 14 of the training materials, the instant specification provides adequate written description for the claims.

Reconsideration and withdrawal of the rejection in view of the foregoing are respectfully requested.

Paragraph 6. Rejection of Claims 107-113 and 121-135 Under 35 U.S.C. § 112, First Paragraph

Claims 107-113 and 121-135 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner states that the claims encompass a sequence that has the recited sequence similarity and the functional property of binding $\alpha 4\beta 7$ integrin. The Examiner further states that there is no disclosure in the specification as to what amino acid residues are important for $\alpha 4\beta 7$ integrin binding. According to the Examiner, the art recognizes that even a single amino acid sequence change can destroy the function of a biomolecule and cites Lederman *et al.* (Reference R, Form PTO 892) as demonstrating the unpredictability of the relationship between sequence and binding function. The Examiner concludes that it would require undue experimentation to practice the claimed invention.

It is well established that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening." In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed". Id. Accordingly, enablement does not require absolute predictability, but that the person of ordinary skill in the art be able to practice the invention without undue experimentation. Id.

The person of ordinary skill in the art would be able to practice the claimed invention following the guidance of the specification and using no more than routine experimentation. Methods suitable for preparing variants of proteins that contain amino acid additions, deletions and/or substitutions were well known in the art at the time the application was filed. The specification discloses and exemplifies a method for identifying fusion proteins that bind $\alpha 4\beta 7$ integrin. Specification at page 74, line 19 *et seq.* Using conventional techniques and the assay disclosed in the specification or other suitable assays the person of skill in the art could readily make the claimed fusion proteins. Screening proteins, such as fusion proteins, to ascertain binding properties is considered routine in the art, and does not constitute undue experimentation. This routine screening is analogous to the screening of hybridomas to identify those hybridomas that produce a desired antibody which the Wands court determined was not undue experimentation. Id.

In regard to the Examiner's remarks concerning which amino acid residues are important for $\alpha4\beta7$ integrin binding, the Examiner's attention is directed to the detailed discussion of MAdCAM structure at page 17, line 30 through page 22, line 24. This discussion points out regions and particular amino acid motifs of primate MAdCAM that are important for $\alpha4\beta7$ integrin binding. In particular, human and macaque MAdCAM are taught to have two amino-terminal immunoglobulin-like domains that are homologous to those of murine MAdCAM, which is a member of the family of immunoglobulin-like adhesion receptors. Specification at page 18, lines 21-26. The specification teaches that domain 1 of murine MAdCAM and ICAM-1, ICAM-2 and ICAM-3, and domains 1 and 4 of VCAM-1 contain a short amino acid motif (G-(I L)-(D E)-(T S)-(P S)-L) that is located between β sheets c and d of the proteins (the C-D loop). Specification at page 19, lines 19-29. The specification further teaches that this GLDTSL motif is also found in the primate MAdCAMs disclosed in the application. Id.

The specification includes a discussion of published studies that demonstrated that mutations in the GLDTSL motif in ICAM-1 or VCAM-1 dramatically affected binding to LFA-1 or $\alpha4\beta7$ integrin, respectively. Id. The specification further teaches that a mutation in the GLDTSL motif in murine MAdCAM abolished interaction with cells that expressed $\alpha4\beta7$ integrin, and that the GLDTSL motif is required for binding of murine MAdCAM to $\alpha4\beta7$ integrin. Id. at page 20, lines 11-19. The specification also teaches that each primate clone disclosed contains "a sequence of nine amino acids (which contains the "LDTSL" motif) in the predicted C-D loop of the Ig-like domain 1, and is implicated as a general integrin recognition site ...." Id. at page 20, lines 31-34.

Thus, the specification teaches the person of ordinary skill in the art that the C-D loop in immunoglobulin-like domain 1, and the GLDTSL motif or LDTSL motif in particular, are important for binding to $\alpha4\beta7$ integrin and that amino acid additions, deletions and/or substitutions in the C-D loop could alter and possibly abrogate binding to $\alpha4\beta7$ integrin. Accordingly, the specification provides ample guidance regarding the structure-function relationship of MAdCAM to support the claims.

In view of the knowledge in the art and the teaching of the specification the enablement requirement of 35 U.S.C. § 112 is satisfied even if some experimentation is required to practice certain embodiments of the invention, because the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Id. Accordingly, any experimentation that is required is not considered undue.

Evidence that fusion proteins comprising variants of primate MAdCAM that bind α4β7 integrin can be prepared using routine procedures that are well known in the art or taught in the specification is presented in the Declaration of Michael J. Briskin, Ph.D. Under 37 C.F.R. § 1.132 that was filed in a related application (Application No. 08/523,004). A copy of the Declaration is provided herewith (An unexecuted Declaration was initially filed on October 5, 1998 and the executed Declaration was filed on October 26, 1998. Our copy of the executed Declaration and transmittal paper that were filed does not include page 1 of the Declaration. Copies of both the unexecuted Declaration and the executed Declaration and transmittal paper that were filed are being provided herewith).

In the Declaration Dr. Briskin describes a study in which a number of fusion proteins comprising portions of human MAdCAM that contained single amino acid substitutions were prepared and tested for binding to α4β7. The mutations were made in portions of human MAdCAM that correspond to regions of other immunoglobulin-like adhesion molecules that are important for integrin binding, namely the CD loop, EF loop, C'E loop and FG loop. Declaration at page 4, lines 22-26. Of the 31 fusion proteins generated, 14 displayed mean binding to α4β7 integrin at 80% to 100% of the control in an adhesion assay. Id. at the Table. Thus, even though the study specifically introduced amino acid substitutions into regions of human MAdCAM that are important for binding to α4β7 integrin, fusion proteins that retained α4β7 binding activity were produced. Under the circumstances, any experimentation required to practice the invention is not undue.

Reconsideration and withdrawal of the rejection are requested.

Paragraph 7. Rejection of Claims 105-112, 115, 116 and 120-135 Under 35 U.S.C. § 112, First Paragraph

Claims 105-112, 115, 116 and 120-135 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

A. The Examiner states that there is no support for the recitation "nucleic acid that shares at least about 75% (or 90%)" in Claims 105, 106, 115 and 116.

The Examiner's attention is directed to the Specification at page 27, line 29 through page 28, line 4, where Applicants' teach:

> In one embodiment, the nucleic acid shares at least about 50% nucleotide sequence similarity to any one of the nucleotide sequences shown in Figure 1, Figure 2, or Figure 3 (SEQ ID NO:1, 3, or 5, respectively) or to one of the MAdCAM coding regions thereof. More preferably, the nucleic acid shares at least about 75% nucleotide sequence similarity, and still more preferably, at least about 90% nucleotide sequence similarity, to any one of the sequences shown in Figure 1, Figure 2, or Figure 3 (SEQ ID NO:1, 3, or 5, respectively) or to one of the MAdCAM coding regions thereof.

B. The Examiner states that there is no support in the specification for the fusion protein of Claims 107-112 and 120-135 which contain i) an $\alpha 4\beta 7$ integrin-binding fragment, ii) wherein the sequence is at least 55%, 75% or 90% similar, or iii) where the fragment is defined as in Claim 108.

With respect to fusion proteins that comprise an $\alpha 4\beta 7$ integrin-binding fragment of primate MAdCAM, a fragment that comprises the entire extracellular domain of primate MAdCAM or a fragment that comprises the two N-terminal immunoglobulin domains of primate MAdCAM (i and iii), the Examiner's attention is directed to the specification at page 16, lines 25-31.

Support for the recited degree of amino acid sequence similarity is found at page 17, lines 23-29.

Reconsideration and withdrawal of the rejection on this basis is requested.

Paragraph 8. Priority

The Examiner states that the currently claimed inventions are not disclosed in parent application 08/386,857 and that the claimed inventions are not entitled to the priority date of said parent application.

The Specification has been amended to correct the Related Applications Paragraph and a Request for Corrected Filing Receipt is being filed concurrently herewith.

Paragraph 9. "similarity"

The Examiner states that the word "similarity" as recited in the claims is not defined in the specification. The Examiner acknowledges that the specification discloses an algorithm suitable for determining amino acid sequence similarity, but states that it is unclear whether the word "similarity" in the claims encompasses other forms of similarity. The Examiner interprets similarity as meaning "containing the same amino acids irregardless [sic] of linear order (e.g. both proteins contain all known amino acids, therefore they have 100% similarity)." Office Action at page 7, lines 7-9.

If the Examiner considered the claims to be unclear in the recitation of the word "similarity" the claims should have been rejected under 35 U.S.C. § 112, second paragraph.

The second paragraph of 35 U.S.C. § 112 requires no more than that the claims set forth and circumscribe the invention with a reasonable degree of particularity and precision. In determining if particular claims meet this standard, the claim language must always be analyzed in light of the teachings of the specification and prior art as it would be interpreted by one possessing ordinary skill in the art. In re Moore and Janoski, 169 USPQ 236 (CCPA 1971).

The Examiner appears to interpret the meaning of "similar" without regard to the context in which the word is used in the claims. For example, at the time the Office Action issued, Claim 103 recited "... the amino acid sequence of said naturally occurring primate MAdCAM is an amino acid sequence that is at least about 75% similar to SEQ ID NO:2, SEQ ID NO:4 of SEQ ID NO:6." Other claims that recite "similarity" use the word in a similar context referring

to either amino acid sequence similarity or nucleotide sequence similarity (Claims 105, 106, 115 and 116). Thus, when the word "similarity" is taken in context, it is clear that the claims refer to amino acid or nucleotide "sequence similarity" and not to any other form of similarity. The term "sequence similarity", or "similarity" when referring to an amino acid or nucleotide sequence, is a term of art that is immediately recognized by those having ordinary skill in the art to mean similarity of amino acid or nucleotide sequences of polypeptides or nucleic acids, respectively, when linear sequences are aligned and compared. The person of skill in the art does not confuse sequence similarity with amino acid composition or nucleotide composition, which the Examiner defines in his statement of rejection (containing the same amino acids regardless of linear order).

The teachings of the specification demonstrate that the person of skill in the art would interpret Applicants' claims as requiring "sequence similarity." First, Applicants disclose algorithms and parameters suitable for determining % similarity of nucleotide and amino acid sequences. Specification at page 48, lines 19-31. Second, the specification includes a discussion of the results of amino acid sequence comparisons of human and murine MAdCAMs, that clearly demonstrates that sequence similarity is distinct from sequence composition. In particular, the specification teaches:

> The next region found in clones 4 and 20 is analogous to the mucin domain of murine MAdCAM-1, due to a prevalence of serine, threonine and proline (69% for clone 4 and 76% for clone 20) residues (boxed in Figure 1 and Figure 2). This region, although similar in amino acid composition to murine MAdCAM-1, is highly divergent from murine MAdCAM-1.

Specification at page 21, lines 13-18 (emphasis added). See also, Specification at page 57, line 32 through page 58, line 19. Thus, the Examiner's interpretation of the meaning of the word "similarity" is contrary to the teachings of the specification.

Based upon the art recognized meaning of sequence similarity and the teaching of the specification, the person of skill in the art would immediately recognize that the word "similarity" in the context of the claims means similarity of amino acid or nucleotide sequences of a polypeptide or nucleic acid, respectively, when linear sequences are aligned and compared. Nonetheless, in order to expedite prosecution, the claims have been amended to more clearly

indicate that similarity refers to amino acid sequence similarity or nucleotide sequence similarity.

Paragraph 11. Rejection of Claim 107-111, 113-116, 118, 120-124 and 126-135 Under 35 U.S.C. § 102(b)

Claim 107-111, 113-116, 118, 120-124 and 126-135 are rejected under 35 U.S.C. § 102(b) as being anticipated by Butcher *et al.* (WO 94 13312). The rejection is based upon the Examiner's interpretation of "similarity" as meaning "containing the same amino acids irregardless [sic] of linear order." Office Action at page 7, lines 18-20.

In view of the remarks set forth above addressing Paragraph 9, which make clear that the amino acid sequence similarity between naturally occurring murine and primate MAdCAMs is not 100%, reconsideration and withdrawal of the rejection are respectfully requested.

Paragraph 12. Rejection of Claims 24-26, 28-32, 102-106, 113-116, 118 and 119 Under 35 U.S.C. § 102(e)

Claims 24-26, 28-32, 102-106, 113-116, 118 and 119 are rejected under 35 U.S.C. § 102(e) as being anticipated by Capon *et al.* (U.S. Patent No. 5,565,335). The Examiner states that MAdCAM as defined in the specification encompasses any molecule with at least one property of MAdCAM (e.g., mediates cellular adhesion). Office Action at page 8, lines 15-17. The Examiner concludes that "'a naturally occurring primate MAdCAM' would encompass primate derived adhesion molecules per se." Id. at lines 17-19. The Examiner interprets "similarity" as meaning containing the same amino acids regardless of linear order. Id.

Independent Claims 24 and 113 have been amended to recite "binds $\alpha 4\beta 7$ integrin" and percent amino acid sequence similarity. As amended, the claims set forth functional and structural features of the fusion proteins comprising primate MAdCAMs which distinguish the claimed fusion proteins from the immunoadhesion fusion proteins disclosed by Capon *et al.*

Reconsideration and withdrawal of the rejection are requested.

Paragraph 14. Rejection of Claims 107-116 and 118-135 Under 35 U.S.C. § 103(a)

Claims 107-116 and 118-135 are rejected under 35 U.S.C. § 103(a) as being obvious over Butcher *et al.* in view of Capon *et al.*

There are several references by Butcher *et al.* and by Capon *et al.* of record. However, the Examiner's statements concerning the teachings of Butcher *et al.* and Capon *et al.* are substantially similar to his statements in Paragraphs 11 and 12 of the Office Action, respectively. Therefore, it appears that this rejection is based on Butcher et al. (WO 94 13312) in view of Capon et al. (U.S. Patent No. 5,565,335). Confirmation for the record is requested in the next Office Communication.

The rejection is based upon the Examiner's interpretation of "similarity" as meaning containing the same amino acids regardless of linear order. Office Action at page 9, line 9 *et seq.*

In view of the remarks set forth above addressing Paragraph 9, which make clear that the amino acid sequence similarity between naturally occurring murine and primate MAdCAMs is not 100%, reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the Related Applications Paragraph on page 1with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

This application is the U.S. National Phase of PCT US96/02153, filed February 12, 1996 and is a continuation-in-part of U.S. Serial No. 08/523,004 (Attorney Docket No. LKS94-04A), filed on September 1, 1995, [which is a continuation-in-part of U.S. Serial No. 08/386,857 (Attorney Docket No. LKS94-04), filed on February 10, 1995,] the teachings of which are incorporated herein by reference in their entirety.

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

Claims 33, 34, 37, 38, 44, 46, 89-93, 94-100 and Claims 102, 104, 110, 114 and 123 have been cancelled without prejudice. Claims 24, 103, 107-109, 113, 120-122, 126, 128, 129, 131, 133 and 134 have been amended and Claims 136-160 are new.

24. (Twice Amended) A fusion protein comprising a naturally occurring primate MAdCAM, wherein said naturally occurring primate MAdCAM binds $\alpha 4\beta 7$ integrin and has at least about 55% amino acid sequence similarity to an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4 and SEQ ID NO:6.

103. (Amended) The fusion protein of Claim 24 wherein [the amino acid sequence of] said naturally occurring primate MAdCAM [is an amino acid sequence that is] has at least about 75% [similar] amino acid sequence similarity to an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4 [or] and SEQ ID NO:6.

107. (Amended) A fusion protein comprising an α4β7 integrin-binding fragment of a naturally occurring primate MAdCAM, wherein [the amino acid sequence of] said primate MAdCAM [is an amino acid sequence that is] has at least about 55% [similar] amino acid sequence similarity to an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4 [or] and SEQ ID NO:6, and said α4β7 integrin-binding fragment comprises the N-terminal immunoglobulin-like domain of said primate MAdCAM.

108. (Amended) The fusion protein of Claim 107 wherein said α4β7 integrin-binding fragment is selected from the group consisting of a fragment comprising the entire extracellular domain of primate MAdCAM and a fragment comprising the two N-terminal immunoglobulin domains of primate MAdCAM[, wherein the amino acid sequence of said primate MAdCAM is an amino acid sequence that is at least about 55% similar to SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:6].

109. (Amended) The fusion protein of Claim 107 wherein [the amino acid sequence of] said primate MAdCAM [is an amino acid sequence that is] has at least about 75% [similar] amino acid sequence similarity to SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:6.

113. (Amended) A fusion protein comprising a naturally occurring human MAdCAM, wherein said naturally occurring human MAdCAM binds α4β7 integrin and [the amino acid sequence of said human MAdCAM is an amino acid sequence that is at least about 55% similar] has at least about 75% amino acid sequence similarity to SEQ ID NO:2 or SEQ ID NO:4.

120. (Amended) A fusion protein comprising an α4β7 integrin-binding fragment of a naturally occurring human MAdCAM, wherein [the amino acid sequence of] said naturally occurring human MAdCAM binds α4β7 integrin and has [is an amino acid sequence that is] at least about [55% similar] 75% amino acid sequence similarity to SEQ ID NO:2 or SEQ ID NO:4,

and said α4β7 integrin-binding fragment comprises the two N-terminal immunoglobulin-like domains of said human MAdCAM.

121. (Amended) The fusion protein of Claim 120, wherein said α4β7 integrin-binding fragment is selected from the group consisting of a fragment comprising the entire extracellular domain of human MAdCAM and a fragment comprising the two N-terminal immunoglobulin domains of human MAdCAM[, wherein and the amino acid sequence of said human MAdCAM is an amino acid sequence that is at least about 55% similar to SEQ ID NO:2 or SEQ ID NO:4].

122. (Amended) The fusion protein of Claim 120, wherein [the amino acid sequence of] said human MAdCAM [is an amino acid sequence that is] has at least about 75% [similar] amino acid sequence similarity to SEQ ID NO:2 or SEQ ID NO:4.

126. (Amended) A fusion protein comprising a primate MAdCAM moiety, wherein said primate MAdCAM moiety has binding[-]affinity for α4β7 integrin and comprises an amino acid sequence selected from the group consisting of SEQ ID NO:2 [,] and the amino acid sequence of an α4β7 integrin-binding portion of the polypeptide shown in Figure 1 (SEQ ID NO:2) [and an amino acid sequence with at least about 55% sequence similarity to either of the foregoing], wherein said α4β7 integrin-binding portion comprises the N-terminal immunoglobulin-like domain.

128. (Amended) The fusion protein of Claim 126 wherein said α4β7 integrin-binding portion is the complete extracellular domain of the polypeptide shown in Figure 1 (SEQ ID NO:2).

129. (Amended) The fusion protein of Claim 126 wherein said α4β7 integrin-binding portion consists of the two amino-terminal immunoglobulin domains of the polypeptide shown in Figure 1 (SEQ ID NO:2).

131. (Amended) A fusion protein comprising a primate MAdCAM moiety, wherein said primate MAdCAM moiety has binding[-]affinity for $\alpha 4\beta 7$ integrin and comprises an amino acid sequence selected from the group consisting of SEQ ID NO:4[,] and the amino acid sequence of an $\alpha 4\beta 7$ integrin-binding portion of the polypeptide shown in Figure [1] 2 (SEQ ID NO:4) [and an amino acid sequence with at least about 55% sequence similarity to either of the foregoing], wherein said $\alpha 4\beta 7$ integrin-binding portion comprises the N-terminal immunoglobulin-like domain.

133. (Amended) The fusion protein of Claim 131 wherein said $\alpha 4\beta 7$ integrin-binding portion consists of the complete extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:4).

134. (Amended) The fusion protein of Claim 131 wherein said $\alpha 4\beta 7$ integrin-binding portion is the two amino-terminal immunoglobulin domains of the polypeptide shown in Figure 2 (SEQ ID NO:4).